CDKL5 deficiency disorder

CDKL5 deficiency disorder is characterized by seizures that begin in infancy, followed by significant delays in many aspects of development.

Seizures in CDKL5 deficiency disorder usually begin within the first 3 months of life, and can appear as early as the first week after birth. The types of seizures change with age, and may follow a predictable pattern. The most common types are generalized tonic-clonic seizures, which involve a loss of consciousness, muscle rigidity, and convulsions; tonic seizures, which are characterized by abnormal muscle contractions; and epileptic spasms, which involve short episodes of muscle jerks. Seizures occur daily in most people with CDKL5 deficiency disorder, although they can have periods when they are seizure-free. Seizures in CDKL5 deficiency disorder are typically resistant to treatment.

Development is impaired in children with CDKL5 deficiency disorder. Most have severe intellectual disability and little or no speech. The development of gross motor skills, such as sitting, standing, and walking, is delayed or not achieved. About one-third of affected individuals are able to walk independently. Fine motor skills, such as picking up small objects with the fingers, are also impaired; about half of affected individuals have purposeful use of their hands. Most people with this condition have vision problems (cortical visual impairment).

Other common features of CDKL5 deficiency disorder include repetitive hand movements (stereotypies), such as clapping, hand licking, and hand sucking; teeth grinding (bruxism); disrupted sleep; feeding difficulties; and gastrointestinal problems including constipation and backflow of acidic stomach contents into the esophagus (gastroesophageal reflux). Some affected individuals have episodes of irregular breathing. Distinctive facial features in some people with CDKL5 deficiency disorder include a high and broad forehead, large and deep-set eyes, a well-defined space between the nose and upper lip (philtrum), full lips, widely spaced teeth, and a high roof of the mouth (palate). Other physical differences can also occur, such as an unusually small head size (microcephaly), side-to-side curvature of the spine (scoliosis), and tapered fingers.

CDKL5 deficiency disorder was previously classified as an atypical form of Rett syndrome. These conditions have common features, including seizures, intellectual disability, and other problems with development. However, the signs and symptoms associated with CDKL5 deficiency disorder and its genetic cause are distinct from those of Rett syndrome, and CDKL5 deficiency disorder is now considered a separate condition.

Frequency

CDKL5 deficiency disorder appears to be a rare condition with an incidence of 1 in 40,000 to 60,000 newborns. About 90 percent of those diagnosed with CDKL5 deficiency disorder are girls.

Causes

As its name suggests, CDKL5 deficiency disorder is caused by mutations in the *CDKL5* gene. This gene provides instructions for making a protein that is essential for normal brain development and function.

Mutations in the *CDKL5* gene reduce the amount of functional CDKL5 protein or alter its activity in nerve cells (neurons). A shortage (deficiency) of CDKL5 or impairment of its function disrupts brain development, but it is unclear how these changes cause the specific features of CDKL5 deficiency disorder.

Inheritance Pattern

This condition is inherited in an X-linked dominant pattern. The *CDKL5* gene is located on the X chromosome, which is one of the two sex chromosomes. In females (who have two X chromosomes), a mutation in one of the two copies of the *CDKL5* gene in each cell causes the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene causes the disorder. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Almost all cases of this condition result from new (de novo) mutations in the *CDKL5* gene that occur during the formation of reproductive cells (eggs or sperm) or in early embryonic development. These cases occur in people with no history of the disorder in their family.

Researchers suspect that the signs and symptoms of CDKL5 deficiency disorder vary in severity in part because of a process called X-inactivation. Early in embryonic development in females, one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. Usually X-inactivation occurs randomly, such that each X chromosome is active in about half of the body cells. This means that about half of cells have an active X chromosome with a *CDKL5* gene mutation, and half have an active X chromosome without the mutation. However, groups of cells that arise from a single original cell have the same copy of the X chromosome inactivated, so the distribution is not exactly half and half. The proportion of neurons in the brain that have the active X chromosome with the mutation helps determine how severe the features of the condition are in a given individual. Females with a higher percentage of neurons with the mutation have more severe signs and symptoms than females with a lower percentage of neurons with the mutation.

Because males have only one X chromosome in each cell, the mutated version of the *CDKL5* gene is active in all cells. Affected males have no normal copies of the gene.

Other Names for This Condition

- CDKL5 deficiency
- CDKL5 disorder
- CDKL5 encephalopathy
- CDKL5-related epilepsy
- CDKL5-related epileptic encephalopathy
- early infantile epileptic encephalopathy 2

Diagnosis & Management

Formal Diagnostic Criteria

- Olson HE, Demarest ST, Pestana-Knight EM, Swanson LC, Iqbal S, Lal D, Leonard H, Cross JH, Devinsky O, Benke TA. Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review. Pediatr Neurol. 2019 Aug;97:18-25. doi: 10.1016/j.pediatrneurol.2019.02.015. Epub 2019 Feb 23. Review.
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Formal Treatment/Management Guidelines

- Müller A, Helbig I, Jansen C, Bast T, Guerrini R, Jähn J, Muhle H, Auvin S, Korenke GC, Philip S, Keimer R, Striano P, Wolf NI, Püst B, Thiels Ch, Fogarasi A, Waltz S, Kurlemann G, Kovacevic-Preradovic T, Ceulemans B, Schmitt B, Philippi H, Tarquinio D, Buerki S, von Stülpnagel C, Kluger G. Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with CDKL5-related epilepsy. Eur J Paediatr Neurol. 2016 Jan;20(1):147-51. doi: 10.1016/j.ejpn.2015.09.001. Epub 2015 Sep 10.
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Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Early infantile epileptic encephalopathy 2
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C4750718/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22CDKL5+deficiency+disorder%22+OR+%22CDKL5+disorder%22

Other Diagnosis and Management Resources

- International Foundation for CDKL5 Research: CDKL5 Centers of Excellence
  https://www.cdkl5.com/cdkl5-centers-excellence/
- Zhu YC, Xiong ZQ. Molecular and Synaptic Bases of CDKL5 Disorder. Dev Neurobiol. 2019 Jan;79(1):8-19. doi: 10.1002/dneu.22639. Epub 2018 Oct 19. Review.
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Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Developmental Disabilities
  https://medlineplus.gov/developmentaldisabilities.html
- Health Topic: Epilepsy
  https://medlineplus.gov/epilepsy.html
- Health Topic: Rett Syndrome
  https://medlineplus.gov/rettsyndrome.html

Genetic and Rare Diseases Information Center

- Atypical Rett syndrome
  https://rarediseases.info.nih.gov/diseases/4694/atypical-rett-syndrome
- CDKL5 deficiency disorder
  https://rarediseases.info.nih.gov/diseases/12173/cdkl5-deficiency-disorder

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Infantile Spasms Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Infantile-Spasms-Information-Page

Educational Resources

- Centers for Disease Control and Prevention: Intellectual Disability Fact Sheet
  https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/IntellectualDisability.pdf
- International Foundation for CDKL5 Research: CDKL5 Disorder: An Introductory Guide
  https://www.cdkl5.com/wp-content/uploads/2017/01/CDKL5_Introductory-Guide.pdf
- MalaCards: cdkl5 deficiency disorder
  https://www.malacards.org/card/cdkl5_deficiency_disorder
- Orphanet: CDKL5-related epileptic encephalopathy
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=505652

Patient Support and Advocacy Resources

- CDKL5 International Registry & Database
  https://www.cdkl5.com/cdkl5-international-registry-database/
- CDKL5 UK
  http://www.curecdkl5.org/
- Citizens United for Research in Epilepsy (CURE)
  https://www.cureepilepsy.org/
- International Foundation for CDKL5 Research
  https://www.cdkl5.com/
- Loulou Foundation (UK)
  https://www.louloufoundation.org/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/cdkl5/
- Telethon Kids Institute (Australia)
  https://rett.telethonkids.org.au/about/cdkl5-disorder/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28CDKL5%5BTI%5D%29+AND+%28%28deficiency%5BTIAB%5D%29+OR+%28disorder%5BTIAB%5D%29+OR+%28encephalopathy%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 2
  http://omim.org/entry/300672

Medical Genetics Database from MedGen

- Early infantile epileptic encephalopathy 2
  https://www.ncbi.nlm.nih.gov/medgen/1663579

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